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Predictive factors and biomarkers for the 2-year outcome of uveitis in juvenile idiopathic arthritis: data from the Inception Cohort of Newly diagnosed patients with Juvenile Idiopathic Arthritis (ICON-JIA) study

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Abstract

Objective. To define predictors for the 2-year outcome in terms of achieving inactivity, subsequent uveitis reactivation and occurrence of uveitis-related complications of JIA-associated uveitis.

Methods. Demographic and clinical parameters and serum samples of JIA-associated uveitis patients enrolled in ICON at $\leqslant$1 year of JIA diagnosis were collected at study enrolment, every 3 months during the first year and subsequently every 6 months. Predictors for the 2-year outcome were evaluated by linear mixed models.

Results. Of 954 JIA patients included, uveitis occurred in 106 up to the first 2-year follow-up, with 98 of them having complete ophthalmological documentation. In 81.8% and 80.0% of patients, uveitis inactivity was achieved at the 1- and 2-year follow-up after uveitis onset, respectively. JIA onset after the age of 5 years, no use of topical corticosteroids, and adalimumab treatment were significantly associated with an inactive uveitis for at least 6 months (n = 57). Correlates for subsequent uveitis reactivation (n = 16, 30.2%) were age at uveitis onset $\leqslant$5 years and active disease (clinical Juvenile Arthritis Disease Activity Score $>$4.5). Uveitis-related complications were present in 29.8% of patients at first uveitis documentation and in 30.7% and 32.8% at 1- and 2-year follow-up, respectively. Older age at JIA onset, short duration between JIA and uveitis onset, high anterior chamber (AC) cell grades, poor visual acuity, and topical steroid use at first uveitis documentation correlated with uveitis-related complications.

Conclusion. In addition to demographic risk factors, JIA disease and uveitis activity scores and adalimumab are significant predictors for the 2-year outcome of JIA-associated uveitis patients.

Key words: adalimumab, DMARDs, juvenile idiopathic arthritis, predictors, uveitis

Rheumatology key messages

- In this prospective study, predictors for the 2-year outcome of uveitis were defined in JIA patients.
- Demographic risk factors, JIA and uveitis activity scores and adalimumab determined the 2-year uveitis outcome.

Introduction

Uveitis is a significant cause of visual morbidity in children with JIA, which is one of the diseases most frequently associated with the condition [1]. According to the International League of Associations for Rheumatology criteria, JIA comprises a heterogeneous group of arthritis of yet unknown cause and with onset before 16 years of age, characterized by joint inflammation lasting $\geqslant$6 weeks [2]. As vision-threatening complications develop in more

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CLINICAL SCIENCE

than half of the JIA-associated uveitis (JIAU) children, there is a high incidence of visual loss, and eye surgery is frequently required [3–5]. Currently, treatment of JIAU comprises topical and systemic corticosteroids, and conventional synthetic and/or biologic DMARDs for achieving inactivity in refractory disease [6, 7].

New developments in genetics and immunology and the analysis of environmental factors are instrumental for better defining, classifying and treating patients with JIA [8]. Indeed, genetic and environmental factors may influence the prevalence of JIA and associated uveitis, as it varies among different geographic regions [9]. Among the JIA categories, uveitis occurs in 10–13% of patients [3, 10], and even at higher percentages in particular subgroups. Known risk factors for uveitis incidence include young age at arthritis onset, oligoarthritis subtype and short disease duration [3, 11]. ANA [3, 12], elevated ESR [13] and carrying certain HLA-DRB1 alleles [14, 15] appeared as risk factors for uveitis occurrence in JIA. Recently, it was suggested that there is a correlation between elevated S100A8/9 and A12 serum levels and intraocular inflammation [16]. Indeed, systemic anti-inflammatory treatment instituted for arthritis may reduce the risk of uveitis onset in JIA patients [10, 17], particularly if given early during the disease course [18].

Biomarkers can be implemented in daily routine to identify JIA patients at particular risk for uveitis occurrence and a complicated disease course, e.g. for achieving disease inactivity or if the disease is subsequently reactivated or complications develop. Based on data from the prospective Inception Cohort of Newly diagnosed patients with JIA (ICON-JIA) study, clinical and laboratory predictors for the 2-year outcome of JIA-associated uveitis were defined in a large cohort of JIA patients.

Methods

Inception cohort of newly diagnosed patients with JIA (ICON)

ICON is an ongoing, multicentre, observational cohort study of patients in whom JIA was diagnosed within 12 months before enrolment and who are to be observed for at least 10 years [19]. JIA was defined according to the International League of Associations for Rheumatology criteria [2]. International League of Associations for Rheumatology diagnoses of all patients were subjected to a review process to validate the JIA category [19].

The study protocol was approved by the ethics committee of the Charité–Universitätsmedizin Berlin. All parents and patients (of 8 years and above) gave their informed consent at study inclusion according to the Declaration of Helsinki. The study reflects the currently applied standard of care in Germany.

Consecutive JIA patients from 11 paediatric rheumatology clinics in Germany were included, reaching ~1/3 of the expected incident JIA cases nationwide during the recruitment period. Demographic and anamnestic clinical data, as well as family history and patient-reported outcomes, were recorded with standardized questionnaires completed by physicians and parents or patients, respectively. Clinical data, treatment and patient-reported data were collected at ICON enrolment, quarterly in the first year of observation and half-yearly thereafter [19], including rheumatological and ocular assessments.

The paediatric rheumatologists assessed the JIA patients at each visit. The clinical assessment included the JIA core set of criteria, such as the active joint count, physician's global assessment of disease activity on a numeric rating scale (21-point numeric rating scale [NRS], 0–10), and whether the disease was clinically inactive according to the Wallace criteria [20]. In addition, the clinical Juvenile Arthritis Disease Activity Score (cJADAS-10) was calculated. The cJADAS-10 (range 0–30) includes physician's global assessment, parent's global assessment and the number of active joints (maximum 10). The cJADAS-10 thresholds proposed by Consolaro and Ravelli [21] for oligoarticular and polyarticular JIA were applied to define disease activity states. The patient or parent reported about overall well-being on a NRS, functional ability by the Childhood Health Assessment Questionnaire (CHAQ).

Laboratory parameters recorded at ICON enrolment included ANA, RF and HLA-B27, whereas ESR, CRP, and S100A12 [16] were determined at enrolment and follow-up visits.

A detailed and regular assessment by cooperating ophthalmologists was performed in all JIAU patients at each time point, including the clinical characterization of uveitis, visual acuity, slit-lamp examination, tonometry, ophthalmoscopy, uveitis-related complications and treatment (ongoing and newly started systemic and topical treatments). Patients were considered to be off treatment if they did not receive medication and did not start a new treatment (e.g. topical corticosteroids) at that visit.

JIAU patients were thoroughly evaluated according to the Standardization of Uveitis Nomenclature [22] with particular attention to disease activity (e.g. inactivity = no anterior chamber (AC) cells in field size 1×1 mm slit beam; grade 0), topical and systemic anti-inflammatory treatment and comprehensive documentation of complications (e.g. synechiae with number of involved quadrants, cataract, macular oedema). Accordingly, anterior uveitis was defined by the primary site of inflammation in the anterior chamber, including iritis and iridocyclitis. Onset of uveitis was described as sudden (typically pain, eye redness), or insidious (asymptomatic) during the attacks. Intraocular pressure >21 mmHg (ocular hypertension) and glaucoma (presence of glaucomatous optic disc damage, or typical visual field loss) were documented. Best-corrected visual acuity was described as logMAR = $-\log_{10}$ visual acuity fraction.

The first ophthalmologic evaluation in ICON patients with uveitis was referred to as first uveitis documentation or uveitis baseline (U-BL), and the subsequent assessment as uveitis follow-up (U-FU). The most recent, regular ICON visit by the paediatric rheumatologist was designated for ophthalmological assessment with a maximum time gap of 4 weeks.

Outcome

The primary outcome of our study was to determine the rate of patients with inactive uveitis for ⩾6 months within 2 years after first uveitis documentation, whether under topical anti-inflammatory medication and systemic DMARD treatment or not. The secondary outcomes of the study included subsequent uveitis reactivation and the presence of uveitis complications. Uveitis reactivation was analysed in patients who attained inactive uveitis for at least 6 months. The association of sociodemographic variables, JIA and uveitis characteristics and treatment with uveitis inactivity ⩾6 months, reactivation and complications was determined.

Statistical analysis

Descriptive statistics were used to describe the distribution of categorical and continuously distributed variables. The primary and secondary outcomes of the study were analysed by generalized mixed linear models to account for the longitudinal data structure and the correlation between assessments within a patient. Furthermore, the grouping variable eye was introduced in the analyses on the eye level as an additional cluster variable. These models result in unbiased effect estimates in the presence of missing data in the follow-up because a patient is not excluded from analysis when an assessment is missing. Clinical and laboratory parameters at baseline (fixed variables) and treatment (time-varying variables) were assessed in terms of their predictive value for achieving the primary outcome.

The association of treatment and JIA disease characteristics with the outcomes was analysed on the patient level. In contrast, uveitis disease characteristics were analysed on the eye level. If uveitis activity, Tyndall, visual acuity and topical CS were reported on the patient level, the data were collapsed for the reporting within a patient by choosing the eye with worse AC cell score (Standardization of Uveitis Nomenclature) for the analysis, and the right eye if the score was similar in both eyes. A *P*-value of <0.05 is considered significant. Data analyses were performed using SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA).

Results

Demographic factors and patient characteristics

A total of 954 JIA patients were included in this study (67.2% female, 54.2% ANA positive, mean age at JIA onset 7.1 (S.D. 4.6) years). Uveitis occurred in a total of 133 patients (13.9%) during the present observation period of the ICON study (mean follow-up of 45.2 (S.D. 22.1) months). In 106 of the patients, uveitis developed up to 2 years after enrolment in ICON. In fact, uveitis occurred before first JIA symptoms in four of the patients (0.4%), before enrolment in 52 patients (5.5%), in another 26 within the first year (2.7%), and in a further 24 within the second year (2.5%) after ICON enrolment. For this study, however, only those 98 (10.3%) patients were included, for whom the detailed uveitis characterization by the ophthalmologist was available (Supplementary Fig. 1, available at *Rheumatology* online). In these patients, observed for a mean period of 36 (S.D. 19.1) months, the uveitis disease course, including uveitis activity and secondary complications, among other uveitis characteristics, could be investigated. This is a representative sample of all 133 patients, as the 98 patients did not significantly differ with respect to sex ($P=0.168$), JIA category ($P=0.653$), ANA positivity ($P=0.692$) and age at JIA onset ($P=0.358$). Of the 98 patients, 76 were female (77.6%), 83 (84.7%) were ANA positive; the mean age at uveitis diagnosis was 5.1 (S.D. 3.0) years, and the mean age at JIA onset was 3.9 (S.D. 3.0) years. JIA categories in patients with and without uveitis are compared in Table 1.

Uveitis characteristics

The first ophthalmological assessment (U-BL) in patients with uveitis took place 3.2 (S.D. 5.3) months after uveitis diagnosis. Anterior uveitis (in 100% of 98 patients) was bilateral in 39.4% at this time point, in 62.7% at 1-year and in 68.7% at 2-year U-FU ($P < 0.001$). Insidious onset of uveitis was documented in 80.7% ($n=79$) of patients at U-BL, correlating with oligoarthritis in 44 (65.7%) of them. Onset of uveitis was acute in another four patients (4.8%) and was unknown in the remaining 14.5%. Mean visual acuity (logMAR) was 0.21 (S.D. 0.30), 0.08 (S.D. 0.17), and 0.11 (S.D. 0.22) at U-BL, 1-year, and 2-year U-FU ($P=0.10$), and logMAR <0.1 was detected in 84.7% at U-BL, in 95.5% at 1-year U-FU and in 93.4% of patients at 2-year U-FU ($P=0.621$).

Achievement of uveitis inactivity ⩾6 months with anti-inflammatory treatment within 2 years after first uveitis documentation

In 81.8% and 80.0% of the JIAU patients, inactivity of uveitis was reported at the 1- and 2-year U-FU, respectively. Uveitis inactivity ⩾6 months within the 2-year U-FU was reported in 57 (58.2%) of 98 JIAU patients, and this was achieved at a mean of 11.5 (S.D. 15.9) months after uveitis diagnosis.

57.5% of JIAU patients received methotrexate at U-BL (for a median of 5.4 months), 73.3% at the 1-year U-FU and 68.7% at the 2-year U-FU in ($P < 0.001$). In addition, adalimumab use increased significantly within the 2 years after U-BL (6.4%, 14.7%, 22.4% at U-BL, 1-year and 2-year U-FU, respectively, $P < 0.001$). At the U-BL, the patients had been treated with adalimumab for 3.1 months (median).

Topical and systemic corticosteroids were used at U-BL in more patients (74.5% and 11.4%, respectively) than at 1-year (48.0% and 10.3%, respectively) or at 2-year U-FU (38.8% and 6.3%, respectively) ($P < 0.001$ for topical steroids) (see Supplementary Tables 1 and 2, available at *Rheumatology* online).

Correlates for uveitis inactivity ⩾6 months' duration

JIA onset after the age of 4 years and uveitis onset after the age of 5 years were significantly associated with ⩾6 months inactive uveitis during follow-up. Furthermore,

Table 1 Demographic and clinical parameters at enrolment of JIA patients with uveitis diagnosis either before or after enrolment

Parameter	Total sample 954	Patients with uveitis onset before enrolment in ICON 56	Patients with uveitis onset after enrolment and until 1-year in ICON 26	Patients with uveitis onset after 1-year and until 2-years in ICON 24	*P*-value
Female, *n* (%)	641 (67.2)	40 (71.4%)	20 (76.9%)	17 (70.8%)	0.444
Age at JIA onset, mean (S.D.), years	7.1 (4.6)	4.9 (3.5)	2.9 (2.0)	3.3 (2.9)	**0.003**
JIA disease duration, median (IQR), months	6.0 (3.0–11.1)	7.0 (4.4–10.9)	2.8 (1.5–6.5)	3.2 (2.3–8.9)	0.142
JIA category, *n* (%)					0.119
Systemic arthritis	35 (3.8)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Oligoarthritis persistent	365 (38.3%)	30 (53.6%)	15 (57.7%)	10 (41.7%)	
Oligoarthritis extended	79 (8.3%)	5 (8.9%)	4 (15.4%)	2 (8.3%)	
Psoriatic arthritis	45 (4.7)	1 (1.8%)	0 (0.0%)	1 (2.6%)	
Enthesitis-related arthritis	100 (10.5)	6 (10.7%)	1 (3.8%)	0 (0.0%)	
Polyarthritis RF positive	15 (1.6)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Polyarthritis RF negative	252 (26.4)	10 (17.9%)	6 (23.1%)	11 (45.8%)	
Undifferentiated arthritis	63 (6.6)	4 (7.1%)	0 (0.0%)	0 (0.0%)	
ANA positive, *n* (% tested)	517 (54.2)	48 (85.7%)	19 (74.4%)	23 (95.8%)	0.249
RF positive, *n* (% tested)	31 (3.3)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
HLA-B27 positive, *n* (% tested)	146 (15.3)	7 (12.5%)	2 (7.7%)	0 (0.0%)	0.358
Physician's global assessment, NRS 0–10, mean (S.D.)	3.8 (2.6)	3.2 (2.1)	4.0 (3.0)	3.6 (2.8)	0.101
Active joint count, mean (S.D.)	4.1 (7.0)	3.8 (4.9)	4.3 (6.8)	3.7 (6.2)	0.093
cJADAS-10, mean (S.D.)	9.8 (6.2)	7.4 (5.1)	10.2 (4.2)	9.2 (5.9)	0.068
ESR, mean (S.D.), mm/h	22.8 (21.7)	23.7 (18.6)	34.1 (2.2)	36.2 (26.3)	0.082
CRP, mean (S.D.), mg/l	9.8 (18.5)	6.6 (11.8)	15.8 (21.5)	17.5 (28.0)	0.238
S100A12, mean (S.D.), ng/ml	337.5 (806.8)	235.4 (370.2)	594.1 (883.9)	405.3 (462.4)	0.137
CHAQ, median (IQR)	0.25 (0–0.88)	0 (0–0.75)	0.88 (0.1–1.63)	0.63 (0.13–1.25)	**0.015**
Patient's global, NRS 0–10, mean (S.D.)	3.0 (2.3)	2.6 (2.4)	3.1 (2.2)	2.5 (1.9)	0.607
Pain, NRS 0–10, mean (S.D.)	3.0 (2.8)	2.1 (2.4)	3.2 (2.3)	2.1 (2.2)	0.102
Uveitis, *n* (%)	133 (13.9%)	56 (100.0%)	26 (100.0%)	24 (100.0%)	

Uveitis diagnosis either before enrolment or after enrolment and until 1 or 2 years in ICON. Data from 98 patients with detailed uveitis characterization by ophthalmologists. *P*-value of less than 0.05 are indicated in bold. CHAQ: Childhood Health Assessment Questionnaire; cJADAS: clinical juvenile arthritis disease activity score; IQR: interquartile range; NRS: numeric rating scale.

adalimumab treatment and no use of topical corticosteroids in the involved eyes during the 2-year observation period were also significantly associated with ⩾6 months inactive uveitis during follow-up (Table 2). We could not find a significant association for the numerous other clinical, laboratory and disease activity parameters at first uveitis documentation or for other anti-inflammatory medications.

A decreasing JIA disease activity (cJADAS-10: OR 0.76; 95% CI: 0.63, 0.92; $P = 0.035$; physician's global: OR 0.92; 95% CI: 0.85, 0.97; $P = 0.046$) during follow-up was significantly associated with sustaining uveitis inactivity.

Correlates for uveitis reactivation

In 16 patients (28% of 57) uveitis was subsequently reactivated after attaining inactive uveitis within 2 years after U-BL. Fifty-three of the 57 patients with uveitis inactivity for ⩾6 months had sufficient follow-up for analysis of predictors (Tables 3 and 4). Subsequent uveitis reactivation ($n = 16$, 30.2%) was associated with age at uveitis onset ⩽ 5 years. An active disease (cJADAS-10 > 4.5) and the use of topical corticosteroids during U-FU were significantly associated with uveitis reactivation.

Uveitis-related complications

Uveitis-related complications were present in 28 patients (29.8% of 98) at U-BL and in 30.7% and 32.8% at 1-, and 2-year U-FU, respectively. During the follow-up period, a total of nine patients (12.9% of 70) without complications at first uveitis documentation developed new uveitis-related complications (Supplementary Table 3, available at *Rheumatology* online indicates changes in eye complications). Patients with eye complications at the first uveitis documentation were more likely to show complications at the 2-year U-FU compared with patients without (73.7% *vs* 13.5%, $P < 0.001$). The number of patients with ocular hypertension increased during the 2-year follow-up (from 0 at U-BL, to two at 2-year U-FU), possibly related also to the topical steroid use in these patients (Table 5). The number of patients with typical inflammation-related eye complications (e.g. optic disc or macular oedema) was slightly reduced during the observation period, which is probably related to the anti-inflammatory treatment. Meanwhile, the number of other eye complications increased only insignificantly, and only one patient required ocular surgery (EDTA chelation for band-keratopathy) during the observation period (Table 5).

Correlates for uveitis complications

Older age at JIA onset, short duration between JIA and uveitis onset, high AC cell grades ⩾2+, the presence of complications and poor visual acuity (high logMAR rates) at first uveitis documentation were significantly associated with the occurrence of uveitis-related eye complications. Treatment with topical steroids was positively associated with the subsequent development of complications (Table 6).

However, no significant correlation was found between achievement of uveitis inactivity ⩾6 months within 2 years after first uveitis documentation and occurrence of uveitis-related eye complications. Nor did the use of conventional synthetic or biologic DMARDs appear to significantly alter the rate of eye complications during the follow-up period. However, combined use of adalimumab and methotrexate showed a lower rate of eye complications in follow-up, but without reaching significance ($P = 0.09$).

Discussion

Achievement of uveitis inactivity and subsequent reactivation

In this ICON study, patient characteristics and demographic risk factors compare favourably with previously published studies [3, 4, 10, 12, 13, 23–25]. Our data show for the first time that patients in whom uveitis inactivity ⩾6 months was achieved with anti-inflammatory medication were significantly older at onset of JIA and uveitis, and the chance to achieve inactivity was particularly high when uveitis had begun after age 5. Herein, gender did not appear as a predictive factor for response to DMARD treatment, or subsequent uveitis reactivation, or development of complications. Previously, male gender was related to good visual outcome [25]. Others found that males had an increased risk of developing complications and worse visual outcome [23, 24, 26, 27], probably related to the notion that, in boys, uveitis more often manifests earlier in the disease course or is more severe, or that there is less awareness of disease occurrence in boys [3, 28]. Others did not find differences in uveitis severity between males and females [29].

ANA positivity is a well-known predictor for uveitis occurrence in JIA patients [3, 11, 12, 18, 30]. In the present study it was not a significant predictor for the 2-year outcome of JIAU, which is in agreement with previous observations [3, 27]. Others found more complications in ANA-negative than in the ANA-positive patients [31, 32], probably related to inadequate uveitis screening of JIA patients.

Elevated ESR appeared as a valid baseline prognostic factor for uveitis occurrence in JIA patients [13, 27, 29, 33, 34]. According to our present data, it did not appear as a useful predictor of the further uveitis course, which is probably influenced by anti-inflammatory treatment instituted for JIA.

Previous data disclosed that S100 serum levels in JIAU patients were higher in patients with active uveitis and suggested that they may reflect eye disease [16]. High S100A12 levels in JIA patients were significantly associated with the risk for uveitis [34]. Our presented data show that S100A12 might not be a useful biomarker for monitoring uveitis activity during the course of JIA, probably influenced by the DMARDs being used to treat the underlying rheumatic disease [35].

Grading AC cells is an important measure of uveitis activity [22], accepted also in JIAU [36] primarily involving the iris and ciliary body [37, 38]. Herein, baseline AC cell grade was not a significant predictor for uveitis inactivity ⩾6 months duration. High AC cell scores and the use of topical corticosteroids at the initial uveitis documentation

Table 2 Association of initial clinical/laboratory parameters with ⩾6 months uveitis inactivity

Parameter	Patients without achievement of uveitis inactivity ⩾6 months until 2-year U-FU in ICON 41	Patients with achievement of uveitis inactivity ⩾6 months until 2-year U-FU in ICON 57	OR; 95% CI; *P* value
Female, *n* (%)	31 (75.6%)	42 (73.7)	1.29; 0.61, 2.75; 0.502
Age at JIA onset, mean (S.D.), years	3.5 (3.3)	4.3 (3.4)	**1.10; 1.02, 1.18; 0.014**
Age at uveitis onset, mean (S.D.), years	4.6 (3.4)	4.7 (2.5)	**1.09; 1.01, 1.19; 0.030**
Uveitis onset >5 years, *n* (%)	10 (24.4%)	19 (33.3%)	**1.84; 1.09, 3.10; 0.023**
Interval between JIA and uveitis onset, mean (S.D.), years	1.0 (1.2)	0.5 (1.4)	0.84; 0.62, 1.12; 0.237
JIA category, *n* (%)			
Oligoarthritis persistent	18 (45.0%)	33 (57.9%)	(Reference)
Oligoarthritis extended	5 (12.5%)	6 (10.5%)	0.62; 0.20, 1.85; 0.375
Psoriatic arthritis	1 (2.5%)	1 (1.8%)	0.81; 0.09, 7.50; 0.852
Enthesitis-related arthritis	4 (10.0%)	3 (5.3%)	0.48; 0.10, 2.24; 0.347
Polyarthritis RF negative	9 (22.5%)	12 (21.1%)	0.90; 0.37, 2.21; 0.816
Undifferentiated arthritis	3 (7.5%)	2 (3.5%)	0.75; 0.14, 4.10; 0.738
ANA positive, *n* (%)	33 (82.5%)	47 (82.5%)	—
HLA-B27 positive, *n* (%)	4 (10.0%)	3 (5.3%)	0.38; 0.11, 1.37; 0.140
Laboratory markers			
ESR, mean (S.D.)	22.1 (16.9)	24.6 (17.6)	1.00; 0.98, 1.03; 0.744
CRP, mean (S.D.)	4.1 (4.8)	6.3 (10.0)	1.03; 0.98, 1.07; 0.248
S100A12, mean (S.D.)	427.4 (679.7)	320.6 (438.8)	0.99; 0.99, 1.01; 0.321
Disease activity			
cJADAS-10, mean (S.D.)	6.7 (5.0)	6.3 (4.0)	1.02; 0.93, 1.12; 0.675
Physician's global, NRS, mean (S.D.)	2.8 (2.6)	2.4 (2.2)	0.95; 0.80, 1.13; 0.554
Number of active joints, mean (S.D.)	2.3 (2.2)	1.9 (2.1)	0.85; 0.73, 1.01; 0.060
Parent's global, mean (S.D.)	1.7 (2.1)	1.2 (1.3)	0.92; 0.71, 1.18; 0.505
Pain, NRS, mean (S.D.)	2.4 (2.7)	1.9 (2.2)	0.98; 0.84, 1.14; 0.763
CHAQ, mean (S.D.)	0.71 (0.88)	0.40 (0.59)	0.69; 0.39, 1.21; 0.191
Uveitis activity, AC cell grade/involved eye, mean (S.D.)	1.23 (0.94)	0.93 (0.72)	1.09; 0.66, 1.79; 0.756
Tyndall/involved eye	2.00 (1.24)	1.61 (1.32)	1.10; 0.81, 1.49; 0.546
Visual acuity/involved eye, logMAR	0.19 (0.23)	0.22 (0.36)	0.75; 0.24, 2.38; 0.626
Any uveitis eye complications	9 (24.3%)	19 (33.3%)	0.89; 0.57, 1.99; 0.848
Anti-inflammatory treatment (time-varying)			
NSAID			0.87; 0.41, 1.83; 0.714
Any DMARD			0.79; 0.40, 1.59; 0.516
MTX			0.66; 0.34, 1.27; 0.209
Etanercept ± MTX			1.65; 0.25, 11.06; 0.608
Adalimumab ± MTX			**1.89; 1.15, 3.73; 0.014**
CS, systemic			2.12; 0.86, 5.20; 0.101
CS, topical in involved eyes			**0.36; 0.20, 0.63; 0.001**

Association of clinical and laboratory parameters at first uveitis documentation and treatment during follow-up (time-varying) with uveitis inactivity for ⩾6 months. *P*-value of less than 0.05 are indicated in bold. AC cell grade = anterior chamber cell grade; CHAQ: Childhood Health Assessment Questionnaire; CI: confidence interval; cJADAS: clinical juvenile arthritis disease activity score; CS: corticosteroids; NRS: numeric rating scale; OR: odds ratio; PedsQL: Pediatric Quality of Life Inventory; U-FU: uveitis follow-up.

Table 3 Association of subsequent uveitis reactivation with time-independent clinical parameters

Parameter	Patients without subsequent uveitis reactivation until 2-year U-FU 37	Patients with subsequent uveitis reactivation until 2-year U-FU 16	OR; 95% CI; *P* value
Female, *n* (%)	26 (70.3%)	12 (75.0%)	0.96; 0.32, 2.91; 0.947
Age at JIA onset, mean (S.D.), years	4.3 (2.5)	3.2 (1.9)	0.89; 0.71, 1.11; 0.289
Age at uveitis onset, mean (S.D.), years	4.1 (1.9)	3.8 (1.7)	**0.91; 0.82, 0.98; 0.039**
Age at uveitis onset >5 years, *n* (%)	15 (40.5%)	3 (18.8%)	**0.67; 0.33, 0.92; 0.034**
Interval between JIA and uveitis onset	0.5 (0.9)	0.6 (0.6)	1.60; 0.70, 3.63; 0.263
JIA category, *n* (%)			—
Polyarthritis RF negative	6 (16.7%)	4 (25.0%)	
Oligoarthritis persistent	24 (66.7%)	9 (56.3%)	
Oligoarthritis extended	4 (11.1%)	1 (6.3%)	
Psoriatic arthritis	0 (0.0%)	1 (6.3%)	
Enthesitis-related arthritis	1 (2.8%)	0 (0.0%)	
Undifferentiated arthritis	1 (2.8%)	1 (6.3%)	
ANA positive, *n* (%)	32 (86.5%)	12 (75.0%)	—
HLA-B27 positive, *n* (%)	2 (5.4%)	1 (6.3%)	1.70; 0.22; 13.17; 0.608

Association of subsequent uveitis reactivation ($n = 16$; 28.1%) with time-independent clinical parameters. Fifty-three of 57 patients with uveitis inactivity for $\geqslant 6$ months had sufficient follow-up for analysis. *P*-value of less than 0.05 are indicated in bold. Due to colinearity and small numbers, JIA subcategory and ANA could not be estimated. OR: odds ratio; U-FU: uveitis follow-up.

Table 4 Association of treatment, change in laboratory markers, and disease activity during follow-up with subsequent uveitis reactivation

Parameter	OR; 95% CI	*P* value
Laboratory marker		
ESR	1.02; 0.92, 1.13	0.738
CRP	0.89; 0.67, 1.19	0.433
S100A12	1.01; 0.98, 1.00	0.203
Disease activity		
cJADAS-10 >4.5	**1.84; 1.18, 7.02**	**0.017**
Physician's global, NRS	0.80; 0.33, 1.96	0.626
CHAQ	0.04; 0.01, 33.51	0.341
Parent's global	1.05; 0.57, 1.93	0.878
Pain, NRS	1.15; 0.70, 1.89	0.58
Uveitis activity, AC cell grade/involved eye	**2.04; 1.27, 3.26**	**0.003**
Tyndall/involved eye	**5.65; 2.09, 15.26**	**0.001**
Visual acuity/involved eye, logMAR	0.60; 0.07, 4.99	0.632
Any uveitis eye complications	1.05; 0.65, 1.48	0.198
Anti-inflammatory treatment		
NSAID	1.41; 0.40, 4.95	0.591
Any DMARD	—	
MTX	—	
Etanercept ± MTX	—	
Adalimumab ± MTX	1.03; 0.26, 4.05	0.966
CS, systemic	1.62; 0.27, 9.77	0.596
CS, topical in involved eyes	**3.47; 1.36, 8.86**	**0.01**

Subsequent uveitis reactivation ($n = 16$; 30.2%) until 2 years of follow-up, after achieving uveitis inactivity $\geqslant 6$ months. *P*-value of less than 0.05 are indicated in bold. AC: anterior cell; CHAQ: Childhood Health Assessment Questionnaire; cJADAS: clinical juvenile arthritis disease activity score; CS: corticosteroids; NRS: numeric rating scale; OR: odds ratio; PedsQL: Pediatric Quality of Life Inventory.

Table 5 Uveitis-related eye complications at first uveitis documentation and at 1- and 2-year follow-up

Eye complication	First uveitis documentation 98	1-year U-FU 87[a]	2-year U-FU 75[a]	*P*-value
Any, *n* (%)	28 (29.8%)	23 (30.7%)	22 (32.8%)	0.845
Band-keratopathy, *n* (%)	2 (2.1%)	2 (2.3%)	1 (1.5%)	0.611
Synechiae, *n* (%)	21 (22.3%)	17 (22.7%)	16 (23.9%)	0.869
Cataract, *n* (%)	7 (7.5%)	7 (9.3%)	9 (13.4%)	0.377
Optic disc oedema, *n* (%)	1 (1.1%)	1 (1.3%)	0 (0.0%)	0.669
Macular oedema, *n* (%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0.484
Ocular hypertension, *n* (%)	**0 (0.0%)**	**0 (0.0%)**	**4 (6.0%)**	**0.01**
Glaucoma, *n* (%)	0 (0.0%)	1 (1.3%)	2 (3.0%)	0.228
Iris rubeosis, *n* (%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0.340
Vitreous haze, *n* (%)	2 (2.1%)	2 (2.7%)	1 (1.5%)	0.900
Any eye surgery, *n* (%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	0.264

[a]Out of 98 patients, data from 87 patients were available at 1-year follow-up, and from 75 patients at 2-year follow-up. *P*-value of less than 0.05 are indicated in bold. U-FU: uveitis follow-up.

were associated with subsequent uveitis reactivation. Accordingly, mild disease was an important predisposing factor for subsequent remission in a previous study [26], and a severe disease and worse visual outcome were previously observed in patients with severe disease at onset [23, 24, 26].

In previous studies, high Tyndall effect reflected a more severe uveitis course in terms of uveitis activity and tissue damage [39]. It is, therefore, conceivable that high Tyndall effect at initial documentation correlated with subsequent uveitis reactivation in the present study.

Previous retrospective results indicated that arthritis and uveitis activity are commonly independent of each other [40], and retrospective analysis did not find a significant relationship between the time point of clinical remission for arthritis and uveitis [41]. Our previous study showed that patients with high cJADAS-10 scores at baseline had a higher risk of uveitis occurrence [18]. Accordingly, our data now show that moderate or high JIA disease activity was a reliable predictor for subsequent uveitis reactivation.

Use of DMARDs is critical for achieving uveitis inactivity. The common use of methotrexate in this study is in agreement with previous publications [1, 42]. Methotrexate was associated with a reduced risk of visual loss in recent studies [10, 43], and also prevented uveitis onset when treatment was commenced early after JIA onset [17, 18]. According to the data presented herein, however, methotrexate was not a predictor for attaining uveitis inactivity.

Recent studies with adalimumab found that uveitis inactivity in methotrexate (combined with topical corticosteroids) non-responders is obtained in $\geqslant$3/4 of patients, improving the subsequent disease course particularly when given early during the JIA course [6, 7, 18, 44]. In our study, under DMARDs (including adalimumab use in up to 22.4% of included cases) uveitis inactivity was documented in 81.8% and 80.0% of the JIAU patients at 1- and 2-year U-FU, respectively, which is in agreement with previous publications. Indeed, our data now point to adalimumab use as an important predictor for achieving uveitis inactivity. Adalimumab has proven to be effective for JIAU [7] and recently received approval for this indication. Recent studies further suggested that treatment with adalimumab reduced the uveitis incidence in JIA patients [10, 18].

Uveitis-related complications and their predictors

In this study, the incidence of uveitis and second eye involvement progressively increased during the first 2 years after JIA onset in up to 2/3 of patients, supporting previous observations [10, 12, 26, 30]. The numbers of uveitis-related complications in JIA given herein during the first 2-year course in ICON are in agreement with recent publications providing longer follow-up [3, 10], and the increasing complication rates during the long-term course commonly reported [3, 4, 12, 28, 31].

Herein, late JIA onset and short duration between JIA and uveitis onset were significant predictors for occurrence of uveitis-related eye complications. Accordingly, higher complication rates were previously also found in patients with late onset of arthritis, with uveitis presenting before JIA onset or with a shorter interval between arthritis and uveitis onset [3, 25, 26, 31, 45], probably related to the longer disease period of insidious onset uveitis without sufficient treatment.

Among the factors analysed herein, significant predictors for uveitis complications were high AC cell score, and presence of complications and poor visual acuity at first uveitis documentation. This is supported by a previous notion, as severity of uveitis at first uveitis documentation was the most significant, independent risk factor for subsequent development of complications [26]. In a previous study, increasing AC cell grade was associated with increased rates of visual loss, while DMARD use was associated with a reduced risk of visual loss [46]. Although high flare values (reflecting intraocular inflammation and also tissue damage) in JIAU patients were associated with poor vision and a higher prevalence of uveitis complications in previous studies [31, 39, 47–49], no

Table 6 Association of initial clinical and laboratory parameters and treatment during follow-up with uveitis complications

Parameter	Patients without uveitis complications $n = 61$	Patients with uveitis complications $n = 37$	OR; 95% CI; P value
Female, *n* (%)	53 (80.3%)	26 (70.3%)	2.30; 0.60, 8.76; 0.224
Age at JIA onset, mean (S.D.), years	3.67 (2.92)	4.68 (3.55)	**1.15; 1.01, 1.32; 0.039**
Age at uveitis onset, mean (S.D.), years	4.62 (2.94)	4.92 (3.01)	1.10; 0.95, 1.27; 0.192
Uveitis onset >5 years, *n* (%)	19 (28.8%)	13 (35.1%)	1.99; 0.81, 4.91; 0.135
Interval between JIA and uveitis onset, mean (S.D.), years	0.96 (1.05)	0.25 (1.56)	**0.48; 0.23, 0.99; 0.046**
JIA category, *n* (%)			
Polyarthritis RF negative	15 (22.7%)	6 (17.1%)	(Reference)
Oligoarthritis persistent	9 (13.6%)	3 (8.6%)	0.77; 0.08, 7.22; 0.822
Oligoarthritis extended	35 (53.0%)	19 (54.3%)	1.03; 0.21, 5.08; 0.968
Psoriatic arthritis	1 (1.5%)	2 (5.7%)	3.07; 0.07, 128.13; 0.554
Enthesitis-related arthritis	3 (4.6%)	3 (8.6%)	2.98; 0.17, 51.69; 0.452
Undifferentiated arthritis	3 (4.6%)	2 (5.7%)	—
ANA positive, *n* (%)	54 (81.8%)	33 (89.2%)	1.86; 0.22, 16.00; 0.572
HLA-B27 positive, *n* (%)	5 (7.6%)	3 (8.1%)	—
Laboratory markers			
ESR, mean (S.D.)	23.40 (16.37)	24.27 (19.30)	1.01; 0.97, 1.05; 0.678
CRP, mean (S.D.)	7.07 (11.13)	4.04 (5.06)	0.95; 0.86, 1.04; 0.275
S100A12, mean (S.D.)	398.29 (608.21)	341.01 (452.86)	0.99; 0.99, 1.01; 0.387
Disease activity			
cJADAS-10, mean (S.D.)	6.33 (4.29)	7.67 (4.17)	1.04; 0.90, 1.20; 0.627
Physician's global, NRS, mean (S.D.)	2.46 (2.14)	2.81 (2.82)	0.95; 0.73, 1.23; 0.685
Number of active joints, mean (S.D.)	2.62 (2.21)	3.42 (2.05)	1.01; 0.69, 1.46; 0.891
Parent's global, mean (S.D.)	1.25 (1.65)	1.44 (1.65)	1.20; 0.92, 1.57; 0.182
Pain, NRS, mean (S.D.)	2.19 (2.31)	2.19 (2.59)	1.10; 0.85, 1.41; 0.477
CHAQ, mean (S.D.)	0.51 (0.71)	0.65 (0.81)	1.54; 0.68, 3.53; 0.302
Uveitis activity, AC cell grade/ involved eye	0.87 (0.70)	1.23 (0.99)	**2.24; 1.16, 4.31; 0.016**
Tyndall/involved eye	1.55 (1.33)	1.96 (1.33)	1.16; 0.77, 1.75; 0.469
Visual acuity/involved eye, logMAR	0.11 (0.14)	0.40 (0.49)	**9.95; 2.16, 45.83; 0.003**
Anti-inflammatory treatment (time-varying)			
NSAID			1.07; 0.36, 3.19
Any DMARDs			0.98; 0.60, 3.25
MTX			1.34; 0.42, 4.23
Etanercept ± MTX			0.94; 0.04, 24.68
Adalimumab ± MTX			0.64; 0.13, 1.09
CS, systemic			1.21; 0.22, 6.60
CS, topical, applications/day in involved eyes			**4.06; 1.63, 10.13**

Clinical and laboratory parameters at first uveitis documentation and treatment during follow-up (time-varying) with uveitis complications. *P*-value of less than 0.05 are indicated in bold. AC cell grade: anterior chamber cell grade; CHAQ: Childhood Health Assessment Questionnaire; cJADAS: clinical juvenile arthritis disease activity score; CS: corticosteroids; NRS: numeric rating scale; OR: odds ratio; PedsQL: Pediatric Quality of Life Inventory.

significant correlation was found for the Tyndall effect in the present study.

In the present study, topical corticosteroid use was significantly associated with the subsequent development of uveitis-related eye complications, particularly cataract formation, which is in accordance with previous reports [5]. Others showed that significantly higher amounts of oral corticosteroids were used in patients with complications [50], while this was not obvious in our study. While the rate of uveitis-related complications was reduced under adalimumab treatment in previous publications [7, 18], our present data disclose only a tendency for a reduced risk for such complications, probably because most complications already existed at the initial study visit and DMARD therapy, or because this analysis was limited to 2 years, and the preferential use of adalimumab in patients with a severe JIAU course. Herein, no effect of conventional synthetic DMARDs on the development of eye complications could be demonstrated, supporting previous findings [26], while DMARDs reduced the risk of hypotony and other complications in a previous study [4].

Synechiae formation at initial presentation is often followed by the development of vision-threatening complications [4, 26, 46], and their presence, AC flare ⩾1+ and

hypotony were associated with vision loss or poor vision during follow-up [4, 26, 43]. Herein, the presence of uveitis-related complications was not a significant predictor for achieving uveitis inactivity under anti-inflammatory treatment or subsequent reactivation.

Our study has some limitations. (i) ICON is an observational study and the analysis of treatment is a challenge. The association between treatment and outcome is biased by the individual treatment decision of the paediatric rheumatologist or ophthalmologist. Patients on a more severe disease course were more likely to be intensively treated. Furthermore, treatment individually starts at different time points depending on the disease course of the patient and it is not possible to define a baseline for comparisons. (ii) We did not collect data about the indication to start treatment. DMARD treatment may be initiated to control the JIA disease activity or the uveitis activity. (iii) The first uveitis documentation does not necessarily reflect the assessment of uveitis activity at the uveitis onset. Treatment may already have started before the first documentation. However, during the recruitment period, an estimated one-third of all new cases with JIA in Germany were included in ICON and examined by paediatric rheumatologists and ophthalmologists in a standardized way, so that representative data on the uveitis outcome and its predictors could be obtained.

In summary, in addition to demographic risk factors, JIA disease and uveitis activity scores and treatment with adalimumab were significant predictors for the 2-year course of JIAU patients in this inception cohort study. Laboratory tests found to be significant biomarkers for uveitis occurrence (e.g. ANA, ESR, S100), however, may lose their respective predictive value for the disease course under the influence of anti-inflammatory treatment instituted early in the JIA course.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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